Challenges and needs in experimental therapies for multiple sclerosis

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Abstract: PURPOSE OF REVIEW Despite dramatic advances in the treatment of people with multiple sclerosis over the last decade, several unmet medical needs still remain and should be approached with new compounds in experimental clinical trials. The prerequisites for successful clinical trials in multiple sclerosis have changed considerably over time and activities have started to improve clinical development of new drugs in several aspects including trial designs, patient selection and outcome parameters. This review will address some of the challenges in early experimental trials in multiple sclerosis and recent approaches in the field. RECENT FINDINGS Highly intensive treatment regimens like autologous hematopoietic stem cell transplantation provide evidence for sustained long-term treatment effects in multiple sclerosis patients. Several different approaches towards neuroprotection and remyelination have entered the clinical phase and demonstrated that stabilization, even improvement of disability is achievable in short-term studies. SUMMARY New therapeutic strategies have entered the clinic with the prospects of long-term efficacy and enduring effects on disability progression.

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REVIEW

Challenges and needs in experimental therapies for multiple sclerosis

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Despite dramatic advances in the treatment of people with multiple sclerosis over the last decade, several unmet medical needs still remain and should be approached with new compounds in experimental clinical trials. The prerequisites for successful clinical trials in multiple sclerosis have changed considerably over time and activities have started to improve clinical development of new drugs in several aspects including trial designs, patient selection and outcome parameters. This review will address some of the challenges in early experimental trials in multiple sclerosis and recent approaches in the field.

Recent findings
Highly intensive treatment regimens like autologous hematopoietic stem cell transplantation provide evidence for sustained long-term treatment effects in multiple sclerosis patients. Several different approaches towards neuroprotection and remyelination have entered the clinical phase and demonstrated that stabilization, even improvement of disability is achievable in short-term studies.

Summary
New therapeutic strategies have entered the clinic with the prospects of long-term efficacy and enduring effects on disability progression.

Keywords
experimental therapy, multiple sclerosis, neuroprotection, outcome measure, trial

INTRODUCTION

Over the last decade we have seen a tremendous increase in the number of approved therapies for multiple sclerosis and these have changed the management of the disease considerably. As a downside of the development, patients have to face increasing and sometimes even severe risks from side effects of highly active disease-modifying therapies. Nevertheless, early treatment initiation has become standard-of-care even in patients with their first manifestation of the disease called clinically isolated syndrome. Recent adaptations in the diagnostic criteria for multiple sclerosis facilitate a definite diagnosis of multiple sclerosis in many patients at this stage and provide the basis for a large spectrum of approved therapies to be initiated [1].

The increasing efficacy of immune therapies fostered new developments in the definition of treatment responses. The term of no evident disease activity (NEDA) has been proposed, which combines disease-free status by clinical parameters (relapses and disability progression) and new lesion development on MRI [2]. A treat-to-target approach using NEDA as target endpoint has been proposed for the management of multiple sclerosis and this concept will clearly set a new benchmark for novel disease-modifying drugs seeking approval for treatment of multiple sclerosis [3].

In the therapeutic management of multiple sclerosis, there is a distinction between the impact of a therapy on inflammatory disease activity, which is generally measured by the occurrence of relapses or the development of new or enlarging lesion on the MRI of the brain and spinal cord and the impact of the treatment on neurodegenerative disease processes, which

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KEY POINTS

- Changing paradigms in the management of multiple sclerosis challenge current procedures of experimental clinical trials.
- Developments of innovative trial designs, sensitive outcome measures and novel parameters for patient stratification are needed to improve clinical development for new therapies.
- Highly intensive therapeutic approaches, like autologous hematopoietic stem cell transplantation have demonstrated enduring efficacy and promise long-term remission of disease activity and even improvement of disability.
- New therapeutic strategies targeting neuroprotection and remyelination have achieved promising results in early-phase clinical trials.

are measured by disability progression and brain atrophy on MRI [4▪]. Novel highly active immune therapies have demonstrated a greater effect on both reduction of inflammatory disease activity as well as reducing the progression of the disease. Recently, ocrelizumab a monoclonal antibody against CD20 on B cells leading to long-term depletion of these cells, was the first disease-modifying therapy to be approved for treatment of primary progressive disease [5].

Still, several unmet medical needs remain in the therapeutic management of multiple sclerosis that should be approached by novel experimental therapies. First, there is a need for improvements in safety profiles that have to go along with a high efficacy of new treatments. Second, new therapies should aim to target the main pathogenic mechanisms with high specificity and ideally restore the deleterious immune response without altering the 'normal' functions of the immune system. Third, there is need for neuroprotective therapies and approaches that facilitate remyelination of inflammatory lesions in the brain and spinal cord. Fifth, there is a need for well tolerated treatments to improve important symptoms in multiple sclerosis such as fatigue, gait disturbance, ataxia, spasticity and others. Finally, all of the above named approaches should be selected for individual patients using objective parameters, thus providing personalized treatment decisions.

Here we will review some of the challenges and pitfalls in experimental therapies for multiple sclerosis and focus on the early phase of clinical development in phase I and phase II trials.

CHALLENGES AND PITFALLS IN EXPERIMENTAL THERAPIES FOR MULTIPLE SCLEROSIS

Over the last 50 years, the efficiency of pharmaceutical development has declined constantly, a phenomenon called Erooms law [6]. Pharmaceutical development is usually split in the preclinical phase and the clinical phase, the latter starting from phase I throughout phase III/IV clinical trials. Considering the advances made in high throughput technologies at different levels, that is, in the preclinical phase, it becomes clear that the translation from preclinical to the clinical phase, that is, phase I/II clinical trials, remain the main bottleneck and most critical phase of pharmaceutical development [7]. In fact, 9 out of 10 novel drug candidates fail at this stage.

Thus, several critical points have to be considered during early phase clinical development for multiple sclerosis. The main aims of early phase I/II clinical trials are to establish the safety and tolerability and to provide a proof-of-concept for the efficacy of the investigational drug. Whenever possible efforts should be made to provide a proof-of-mechanism of the approach to confirm the presumed mode of action (MoA) of the therapy. This requires a solid understanding of the presumed MoA and the technologies to proof it with biomarkers of treated patients.

Selection of the most appropriate patients for the specific therapeutic approach is crucial in the early phase clinical development. For novel immune therapies, the recruitment of multiple sclerosis patients to phase II clinical trials is increasingly challenged by the augmenting number of approved therapies. One also has to consider that the observed disease activity in clinical trials has changed over time, which is reflected by the strong differences in the on-treatment relapse rates in clinical trials performed during the last decade [8▪]. The key data used for calculation of effect sizes, patient numbers and observation periods for a specific outcome parameter have to reflect such developments. For example, the annualized relapse rate (ARR) is frequently used as outcome parameter for inflammatory disease activity in clinical trials and recent phase III trials reported ARR less then 0.3 even in the placebo-treated patients [9]. In particular, for therapies aiming at neuroprotection incorrect estimation of disability progression in the trial population has contributed to the failure of proof-of-concept (PoC) trials [10].

One of the most important challenges in experimental therapies in multiple sclerosis is the choice of clinical and imaging-based outcome parameters that allow for the precise quantification of inflammatory disease activity and changes in disability

progression or neurodegeneration [4▪]. Relapses and lesion development on MRI are the main clinical and imaging parameters used for assessment of inflammatory disease activity whereas disability progression and brain atrophy on MRI are the most widely used parameters to reflect neurodegeneration. Novel disease-modifying therapies aim at preventing both, inflammation and neurodegeneration but an increasing number of substances are tested as purely neuroprotective agents. Particularly, early phase experimental therapies are often limited in the duration of the trial and the number of participants. Thus, they have to rely on outcome parameters that are sensitive to changes within those restrictions and provide a surrogate for mid-term and long-term effects of the intervention. In early phase II trials, imaging-based parameters are frequently used as surrogate to follow inflammatory disease activity and/or neurodegeneration. However, with recent highly active immune therapies and novel approaches for neuroprotection and remyelination, there is a fundamental change in these concepts and a clear need for sensitive parameters able to reflect even an improvement in disability. The currently used clinical rating scale to assess disability in multiple sclerosis, the Expanded Disability Rating Scale (EDSS), is largely influenced by walking disability and does not reflect changes in other functional systems (i.e. motor function of upper limb, coordination, fatigue) once an impairment in gait has been reached [11]. Outcome measures based on the EDSS or a composite of EDSS and other measures of the function of the upper extremity (Nine-hole-peg test), walking speed (Timed 25-foot walk test) and cognition (Paced auditory serial attention test or symbol digit modalities test) are, therefore, insensitive to disability outcomes once patients have a reached a certain level of gait impairment. As an example, a trial of natalizumab in secondary progressive multiple sclerosis failed in its primary endpoint, despite a clinical significant improvement in the function of the upper extremity (9-HPT) in the natalizumab-treated group (Steiner *et al.*, 2016). Several groups have started to adapt clinical measures of disability progression and improvement, but further efforts are needed to improve the validity and reliability of clinical outcome measures and test them in innovative trial designs.

EXPERIMENTAL IMMUNE THERAPIES

Recent therapeutic developments have focused on therapies with a long-term impact on the disease. Indeed, highly active therapies like Aletuzumab, Ocrelizumab and Cladribine have shown to effectively reduce disease activity and in some patients even with a longer lasting effect, but still only 30–50% of patients reach complete freedom of disease activity (NEDA) at 2 years [12▪,13].

In the last 24 months, one experimental therapeutic approach has particularly impacted the field, which is autologous hematopoietic stem cell transplantation. The main concept behind the approach is that the intense immunosuppression followed by infusion of autologous hematopoietic stem cells incites a complete replacement of the 'autoreactive' immune system with a new and tolerant immune system [14▪]. In fact, there is experimental data supporting the concept of a complete renewal of the adaptive immune response [15]. Several recent trials have demonstrated very good efficacy of the treatment and corroborated a long-lasting reduction or even complete prevention of new disease activity together with improvements in disability [13,16–20,21▪,22]. Up to 70% of multiple sclerosis patients treated by autologous haematopoietic stem cell transplant (aHSCT) reach a NEDA endpoint at 5 years, thus being far more effective compared with approved therapies [12▪]. Still, it has to be considered that the study populations from pivotal phase III clinical trials of approved therapies are not directly comparable with the smaller phase II studies on aHSCT and a direct comparison of the efficacy and long-term effects of the treatments within controlled clinical trials is warranted. Nevertheless, a recent retrospective analysis of multiple sclerosis patients treated by aHSCT demonstrated efficacy for prevention of further accumulation of disability, and some patients even had an improvement in disability, despite the fact, that most patients already had reached higher disability scores at the time of aHSCT [21▪].

EXPERIMENTAL THERAPIES TARGETING NEUROPROTECTION

Despite some successes in efficacy of anti-inflammatory immune therapies for patients with progressive multiple sclerosis, there is a strong need for agents with neuroprotective properties. Several different pathways are described to be involved in neurodegeneration in multiple sclerosis, including loss of trophic support in demyelinated axons and exposure to inflammatory mediators, reactive oxygen species, mitochondrial dysfunction and changes in the expression sodium channels, which are reviewed elsewhere in more detail [23]. Different available drugs, approved for various indications, target many of these mechanisms and have thus a potential capacity for neuroprotection in multiple sclerosis patients [24]. Such a repurposing of drugs is an efficient way for development of neuroprotective

agents and different academic groups have followed some of these approaches [25]. A recent phase II study tested simvastatin in secondary progressive multiple sclerosis [26,27]. The simvastatin-treated group had a 43% reduction in whole-brain atrophy and a slower worsening of disability measured by EDSS. In a secondary analysis of the trial population, there was evidence for a positive effect of simvastatin on frontal lobe function and physical quality-of-life measurement [26]. Biotin was tested in progressive multiple sclerosis patients in a phase II study using as a novel trial endpoint, which is the proportion of patients with reversal of disability at month 9 confirmed at month 12 [28▪]. A total of 12.6% of high-dose biotin-treated patients achieved the primary endpoint versus none of the placebo group. Following these positive results, a phase III trial in progressive multiple sclerosis patients is ongoing. Phenytoin was tested as neuroprotective agent in a phase II trial in patient with optic neuritis using optical coherence spectroscopy (OCT) to measure the retinal nerve fibre layer thickness (RNFL) of the affected eye at 6 months as primary outcome [29]. Among 86 recruited patients, there was a 30% reduction in the extent of RNFL loss with phenytoin compared with placebo. Ibudilast a phosphodieseterase and macrophage inhibitory factor inhibitor, was tested in a randomized, placebo-controlled phase II clinical trial in 255 progressive multiple sclerosis patients using the change in brain atrophy on MRI, measured by brain parenchymal fraction, as primary outcome parameter. The results were presented at the Congress of the European Committee for Treatment and Research in multiple sclerosis (ECTRIMS, 2017) and the study met the primary endpoint with a 48% reduction in whole brain atrophy after 96 weeks in the ibudilast-treated group [30]. Erythropoietin (EPO), is part of a endogenous neuroprotective system in the brain, with antiapoptotic, anti-inflammatory and antioxidative properties and has been used successfully in a phase II trial in patients with optic neuritis as well as patients in chronic progressive multiple sclerosis patients [31,32]. A recent trial, however, failed to show efficacy of EPO in reducing disability progression measured by a composite measure of maximum gait distance, hand dexterity and cognition from baseline to 24 weeks in progressive multiple sclerosis patients [33].

EXPERIMENTAL THERAPIES TARGETING REMYELINATION

A few new approaches that target remyelination in multiple sclerosis have entered the clinical phase [34,35]. LINGO1 is a glycoprotein expressed on neurons and oligodendrocyte precursor cells and has been identified as important negative regulator of remyelination. A monoclonal antibody (Opicinumab) blocking LINGO1 was developed to facilitate remyelination in multiple sclerosis lesions. Although initial PoC trials did not meet the expected results, posthoc analyses of the trials suggested positive effects in a subgroup of patients with short-disease duration and defined MRI imaging characteristic on magnetization transfer ratio and diffusion weighted images [36,37]. A ongoing phase II clinical trial will assess the efficacy of opicinumab to improve clinical disability in multiple sclerosis patients on stable immune therapy. Another approach targeting remyelination by stimulating the differentiation of oligodendrocyte precursor cells was discovered in a high throughput approach [38]. In a phase II randomized crossover trial twice daily, clemastine was compared with placebo in patients with multiple sclerosis and chronic demyelinating optic neuropathy [39▪]. The primary endpoint was changed in latency delay on VEP, which was reduced by 1.9 ms/eye in the clemastine-treated group.

CONCLUSION

The last decade has brought incredible achievements in the treatment of multiple sclerosis, and new therapeutic concepts targeting NEDA or improvement of disability are already beginning to influence the management of multiple sclerosis patients. Treatment development in multiple sclerosis has to tackle several challenges and pitfalls to successfully pass early phase clinical development and some trials have already demonstrated how they can be overcome to provide new therapies for people with multiple sclerosis.

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